REMARKS

1. *History*

Applicants thank Examiner Yao for the telephonic interview of January 17, 2007. During the interview, Applicants discussed the prior art cited in the Final Office Action.

Claims 1-10, 12, 14-19, 59-66, 68, and 70-74 are presently pending. Claims 1-9 and 59-65 were deemed allowable in the Office Action dated May 3, 2006 ("Non-Final Office Action"). Applicants gratefully acknowledge the withdrawal of all prior rejections and the allowance of claims 1-9 and 59-65.

The outstanding issues are addressed individually below.

2. *The Claims Are Not Obvious Over Meschini In View Of Fanger And Heidenthal*

Claims 10, 12, and 14-19 stand rejected as being unpatentable over Meschini *et al.* ((2000) *Int. J. Cancer* 87: 615-628) ("Meschini") in view of Fanger *et al.*, (U.S. Patent No. 5,762,930) ("Fanger") and Heidenthal *et al.* ((1999) *Biochem. Biophys. Res. Comm.* 267: 49-53) ("Heidenthal"). The Final Office Action restates the rejections detailed in the Non-Final Office Action (see Final Office Action, pg. 2-3). More specifically, the Final Office Action alleges that Meschini teaches a method of detecting cell surface expression of vimentin and that cell surface expression is associated with multidrug resistance (see Final Office Action, pg. 2-3). The Final Office Action also alleges that Fanger teaches administration of LDL to a patient and Heidenthal teaches LDL binding to vimentin (see Final Office Action, pg. 2). The Final Office Action cites an additional reference, entitled "Paraformaldehyde Fixation of Cells," Iowa State University ("Iowa State"), as allegedly supporting the contention that Meschini teaches detection of vimentin binding agent specifically bound to cell surface-expressed vimentin (see Final Office Action, pg. 4). Applicants respectfully traverse this rejection.

For a claimed invention to be obvious under 35 U.S.C. § 103, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)). Moreover, it is improper to combine references where the references teach away from their combination (see MPEP § 2145 (X)(D)(2)).

Applicants' claim 10 is directed to a method for detecting a multidrug resistant cell in a patient in which *cell-surface-expressed* vimentin is detected by a vimentin binding agent that specifically binds to vimentin.

Meschini teaches the detection of *intracellular* vimentin expression (see Meschini *et al.*, p. 618). Meschini does not teach or suggest the detection of *cell-surface-expressed* vimentin.

The Fanger reference teaches generally the administration of LDL modifying agents, or modified LDL, to patients to improve the uptake of LDL by monocytes. This reference does not teach or suggest the detection of *cell-surface-expressed* vimentin, nor that *cell-surface-expressed* vimentin is a measure of multidrug resistance of a tumor.

Heidenthal teaches that modified LDL binds to denatured vimentin *in vitro* (see Heidenthal *et al.*, p. 51). Heidenthal does not teach or suggest the detection of *cell-surface-expressed* vimentin. Heidenthal also does not teach or suggest that LDL binds to native vimentin *in vivo*.

Applicants respectfully assert that the references do not teach or suggest the detection of *cell-surface-expressed* vimentin. As the primary reference cited in the Office Action, Meschini is limited to the detection of *intracellular* vimentin (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶¶ 6-9). Meschini fails to teach or suggest that vimentin is localized to the cell surface because the reference does not show any direct or indirect evidence establishing that vimentin expression is found on the cell surface (see *id.*). For instance, Figure 2 does not show any detectable levels of cell surface-expressed vimentin, but instead shows fluorescent detection of intermediate filaments (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 8). In fact, the only experiments showing cell surface expression of a protein are directed to PgP (P-glycoprotein or P-gp) expression shown in Figure 4 (see Figure 4; the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 8). In this figure, the control shows no fluorescence in the cells, while the experimental results show that the cells have significant fluorescence ringing the periphery of the cells (see Figures 4b and 4c; Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 8). This pattern of fluorescence is indicative of cell-surface-expressed proteins, and is missing from the results shown for vimentin in Figure 2, where there is no visible fluorescence at the periphery of the cells; in Figure 2 the entire detectable signal is located *within* the cell (see the Declaration of Dr. Benquet enclosed herewith

as Exhibit A, ¶ 8). Thus, one of ordinary skill in the art would understand that Figure 2 establishes *intracellular* expression of vimentin, but would not read Meschini as teaching or suggesting the presence of cell-surface-expressed vimentin. In fact the two fluorescence staining experiments for P-gp and vimentin in Meschini's manuscript show clearly the difference between surface (membrane bond) and intracellular protein localization. On the one hand, staining of P-gp (a well established transmembrane protein) shows a clear membrane bound or ring staining of cells; while staining of vimentin shows intracellular staining, in the absence of a ring or membrane bound staining.

Furthermore, one of ordinary skill in the art would read Meschini as teaching away from surface expression of certain cytoskeletal markers. Meschini explicitly teaches the detection of vimentin, cytokeratin, actin, and tubulin, all of which are expressed in cytoskeletal networks located *within* the cell (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 6-9). One of ordinary skill in the art would understand that the authors are labeling intermediate filaments, actin filaments, and microtubules, all of which are components of the cytoskeleton, which is an internal scaffolding located in the cytoplasm *within* the cell (see id.). One with skill in the art would not be taught, or expected, to find such cytoskeletal markers on the cell surface. Not only does Meschini fail to teach or suggest the detection of *cell-surface-expressed* vimentin, but in fact, it teaches away from this concept.

To support its contentions regarding Meschini, the Final Office Action cites the Iowa State reference to establish that fixation is used when labeling cell surface antigens (see Final Office Action, pg. 4). However, the Iowa State reference teaches that the cells are fixed *after* they have been labeled (see Iowa State, pg. 2). The procedure taught in this reference is used to preserve the fluorochrome-conjugated antibody labeling for up to one week, which provides flexibility and safety to the researcher (see Iowa State, pg. 1). There is good reason for fixing cells *after* the labeling procedure — "[f]ixed cells have a permeable membrane" and label "would enter all of the cells" (see Iowa State, pg. 1). Paraformaldehyde fixation is a well-known cytotoxin, and those of ordinary skill in the art would not use paraformaldehyde fixation to label cell-surface-expressed proteins (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 10). Meschini recognizes this, and teaches a protocol for detection of cell surface PgP that does not use fixation, thus not enabling the label to enter the cell (see id.). In contrast, for *intracellular* intermediate filament detection, Meschini uses 2% paraformaldehyde to fix the

cells, and then labels the cells with fluorescein-conjugated antibodies prepared in Nonidet P-40, which is also a permeabilizing agent (see Meschini, pg. 616, *Flow cytometry*). Such a protocol is designed to label intracellular vimentin, with little regard for labeling cell-surface-expressed vimentin (see id.). Therefore, the Iowa State reference does not support the contention that the procedure taught in Meschini was used, or could be used, for the detection of cell-surface-expressed vimentin.

Additionally, Heidenthal does not teach or suggest the binding of LDL to *cell-surface-expressed* vimentin. Nor does Heidenthal teach or suggest the binding of LDL to native vimentin *in vivo*. In fact, the authors state that vimentin isolated from the cells being studied may be from *within* the cells (Heidenthal *et al.*, pg. 52). Furthermore, Heidenthal is limited to teaching that LDL binds to denatured vimentin *in vitro*.

The Fanger reference is limited to the administration of modified LDL or agents that modify LDL to patients to improve the uptake of LDL into monocytes. It does not teach or suggest the use of labeled LDL to bind to *cell-surface-expressed* vimentin, nor that *cell-surface-expressed* vimentin is a measure of neoplastic state of the cell or multidrug resistance of a tumor.

Thus, the references cited in the Final Office Action, alone or in combination, do not teach or suggest the detection of *cell-surface-expressed* vimentin using a vimentin-binding agent that specifically binds to *cell surface-expressed* vimentin.

Likewise, claims 12 and 14-19, which are dependent from claim 10 and contain all of the limitations thereof, are not obviated by these references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

2. The Claims Are Not Obvious Over Thomas In View Of Fanger And Heidenthal

Claims 66, 68, and 70-74 also stand rejected as being unpatentable over Thomas *et al.* ((1999) *Clin. Can. Res.* 5: 2698-2703) ("Thomas") in view of Fanger and Heidenthal. More specifically, the Final Office Action restates the rejections detailed in the Non-Final Office Action (see Final Office Action, pg. 4-5). The Final Office Action alleges that Thomas suggests a method of detecting cell surface expression of vimentin in progressive breast cancer, admitting

that Thomas does not explicitly teach the method of detecting cell surface-expressed vimentin (see Final Office Action, pg. 5). The Final Office Action also opines that Figure 3 in Thomas shows vimentin located on the cell surface (see pg. 5). The Final Office Action also alleges that Fanger teaches administration of LDL to a patient and Heidenthal teaches LDL binding to vimentin (see Final Office Action, pg. 2). In support of its contentions, the Final Office Action cites an additional reference, Moisan *et al.* (2006) *J. Leuk. Biol.* 79: 1-10 ("Moisan"), as allegedly showing that one of ordinary skill in the art would have understood that vimentin is expressed on the surface of abnormally growing or stressed cells (see Final Office Action, pg. 5). Applicants respectfully traverse this rejection.

As stated above, for a claimed invention to be obvious in light of the prior art, the references forming the basis for an obviousness rejection must teach or suggest all of the claim limitations of the claimed invention. (*In re Royka*, 490 F.2d 981 (C.C.P.A. 1974)). Moreover, it is improper to combine references where the references teach away from their combination (see MPEP § 2145 (X)(D)(2)).

Applicants' claim 66 is directed to a method for detecting a neoplastic cell in a patient using a vimentin-binding agent to specifically bind to *cell-surface-expressed* vimentin.

Thomas teaches detecting vimentin expression in intermediate filaments located *within* whole tissues isolated from cancer patients. This reference does not teach or suggest the detection of *cell surface-expressed* vimentin using a vimentin-binding agent to determine whether a cell is neoplastic.

As described above, Fanger generally teaches the administration of LDL or AcLDL to patients. Fanger does not teach or suggest that vimentin expression is found at the cell surface, nor that cell-surface-expressed vimentin is indicative of a neoplastic cell or is a measure of neoplastic potential. Furthermore, this reference does not teach or suggest that the detection of *cell-surface-expressed* vimentin using vimentin-binding agents that specifically bind to *cell-surface-expressed* vimentin.

As described above, Heidenthal teaches that modified LDL binds to *cell-surface-expressed* vimentin (see Heidenthal *et al.*, pp. 51). Heidenthal does not teach or suggest that *cell-surface-expressed* vimentin is indicative of a neoplastic cell or is a measure of neoplastic potential. This reference also does not teach or suggest that the detection of *cell-surface-*

expressed vimentin using vimentin-binding agents that specifically bind to *cell-surface-expressed* vimentin.

Applicants assert that one of ordinary skill in the art would read Thomas as teaching the detection of vimentin *within* cells, not that *cell-surface-expressed* vimentin had been detected (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 13). Specifically, Thomas describes the expression of keratin and vimentin intermediate filaments (see Thomas, pp. 2700-2701; the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 13). Throughout the article, Thomas explicitly teaches that the vimentin staining is showing "keratin [intermediate filaments] and vimentin [intermediate filaments]" (see Figure 1; see also pp. 2700-2701). Figures 1 and 3 are also clearly drawn to showing *intracellular* expression of vimentin (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 13). Figures 1 and 3 show intermediate filament staining, and the authors explicitly teach that such a conclusion is to be drawn from the figures (see *id.*). Therefore, neither figure shows cell surface expression of vimentin (see id.).

Moreover, the authors do not suggest that there is cell surface expression of vimentin (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 13). On the contrary, the authors teach that "our study further suggests that it is the ratio of vimentin to keratin IF coexpression [intermediate filament] that predicts patient survival" (see Thomas, Discussion, pg. 2702). Therefore, Thomas teaches away from the conclusion that vimentin is expressed on the cell surface.

Applicants further aver that Moisan does not provide the teaching to one of ordinary skill in the art that cell surface expression of vimentin could be used as a marker for cancer. Moisan was studying normal neutrophils undergoing apoptosis, which is a normal cell process that is not seen in cancer cells (see the Declaration of Dr. Benquet enclosed herewith as Exhibit A, ¶ 14). Furthermore, neutrophils are normal cells that do not have the characteristics or behavior of cancer cells (see id.). One of ordinary skill in the art would not be inclined to look to this article for potential markers for the detection of cancer because Moisan studies normal cells to elucidate normal cellular processes and behavior (see id.).

Heidenthal also does not teach or suggest the detection *cell-surface-expressed* vimentin. As described above, this reference is limited to teaching that LDL binds to denatured LDL *in vitro*.

Fanger does not teach or suggest the use of labeled LDL to bind to *cell-surface-expressed* vimentin, nor that *cell-surface-expressed* vimentin is a measure of neoplastic state or multidrug resistance of a tumor.

The combination of these references does not result in Applicants' claim 66, which requires administering to a patient and detecting a vimentin-binding agent that specifically binds to cell surface-expressed vimentin present on a neoplastic cell in the patient. Likewise, claims 68 and 70-74, which are dependent on claim 66, and thus contain all the limitations thereof, are also not obviated by the combination of these references.

Accordingly, Applicants respectfully request that this § 103 rejection be reconsidered and withdrawn.

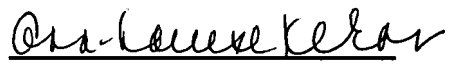
CONCLUSIONS

In view of the arguments set forth above, Applicants respectfully submit that the outstanding rejections contained in the Office Action mailed on November 2, 2006 should be reconsidered and withdrawn.

The time for responding to this action has been extended to March 2, 2007 by the accompanying Petition for a Three Month Extension of Time and payment of fee. No additional fees are due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

If the Examiner believes that any further discussion of this communication would be helpful, please contact the undersigned at the telephone number provided below.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Georges *et al.*	Art Unit:	1642
Serial No.:	10/736,889	Examiner:	Yao, Lei
Filing Date:	December 15, 2003	Customer No.	23483
Title:	**Vimentin Directed Diagnostics and Therapeutics for Multidrug Resistant Neoplastic Disease**	Conf. No.	5738

Exhibit A